D.8 Tricuspid regurgitation – right ventricular function on cardiac MRI

Reference	Park 2016[211]
Study type and analysis	Prospective cohort study Multivariate/univariate Cox proportional hazards model (depending on prognostic factor) South Korea
Number of participants and characteristics	N=75 RV ejection fraction (RVEF) per 5% higher (continuous variable) on cardiac magnetic resonance (CMR) imaging, n=75 RVEF <46% on CMR, n=23 RVEF ≥46% on CMR, n=52 RV end-systolic volume index (RV-ESVI) per 10 ml/m^2 higher (continuous variable) on CMR, n=75 RV-ESVI ≥76 ml/m^2 on CMR, n=50 RV-ESVI <76 ml/m^2 on CMR, n=25 RV end-diastolic volume index (RV-EDVI) on CMR – continuous variable but increment used is unclear, n=75 Tricuspid regurgitation (TR) fraction on CMR – continuous variable but increment used is unclear, n=75 Severe isolated functional TR and underwent isolated TR surgery. Surgery performed by experienced surgeons with >100 cardiac surgeries annually for at least 5 years prior to the study. Of those included, 59 (78.7%) had tricuspid valve replacement and 16 (21.3%) had tricuspid annuloplasty with or without valvuloplasty. No concomitant procedures on other valves were performed at the time of the tricuspid procedures. **Inclusion criteria:** Severe functional TR (TR jet area >30% of right atrial area, inadequate coaptation of tricuspid valve leaflets and systolic flow reversal in hepatic veins).

Exclusion criteria:
Haemodynamically significant primary TR based on imaging, surgical and pathological findings (TR occurring due to structural changes in the tricuspid valve leaflets and chordae as a result of several disease origins, such as rheumatic or degenerative valve disease or congenital, infections, traumatic or iatrogenic causes); coronary disease requiring intervention based on preoperative angiographic findings.

Values listed below are presented as mean (SD) or number (%)

- Age: 59.3 (8.9) years
- Male/female: 14/61 (18.7%/81.3%)
- Body mass index: 21.9 (2.9) kg/m^2
- Body surface area: 1.53 (0.15) m^2
- Systolic blood pressure: 119 (16) mmHg
- Diastolic blood pressure: 67 (10) mmHg
- NYHA class:
  - I, 2 (2.6%)
  - II, 32 (42.7%)
  - III, 36 (48.0%)
  - IV, 5 (6.7%)
- Type of index TR surgery:
  - Tricuspid valve replacement, 59 (78.7%)
  - Tricuspid annuloplasty, 6 (8.0%)
  - Tricuspid annuloplasty + tricuspid valvuloplasty, 10 (13.3%)
- Combined maze operation, 17 (22.7%)
- Rhythm:
  - Sinus, 14 (18.7%)
  - Atrial fibrillation, 61 (81.3%)
- Beta-blockers, 15 (20.0%)
- Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, 13 (17.3%)
- Digoxin, 47 (62.7%)
- Loop diuretics, 44 (58.7%)

	• Spironolactone, 49 (65.3%) • Thiazide, 18 (24%) • Haemoglobin level: 12.3 (1.7) g/dL • Glomerular filtration rate: 64.6 (20.6) ml/min/1.73 m^2 • RV end-diastolic area on echo: 31 (7) mm^2 • RV end-systolic area on echo: 17 (5) mm^2 • RV fractional area change on echo: 46 (8)% • RV diameter on echo: 47 (7) mm • LV end-diastolic diameter on echo: 48 (6) mm^2 • LV end-systolic diameter on echo: 28 (11) mm^2 • LV ejection fraction on echo: 57 (8)% • TR fraction on echo: 35 (20)% • Median (IQR) TR fraction on echo: 39 (25-48)% • Pulmonary artery systolic pressure on echo: 39.6 (10.9) mmHg • RV-EDVI on CMR: 175 (61) ml/m^2 • RV-ESVI on CMR: 98 (46) ml/m^2 • RVEF on CMR: 48 (9)% • LV-EDVI on CMR: 95 (28) ml/m^2 • LV-ESVI on CMR: 45 (21) ml/m^2 • Cardiac index on CMR: 3.7 (1.1) $l/min/m^2$ • TR fraction on CMR: 46 (16)% • Median (IQR) TR fraction on CMR: 49 (33-60)% **Population source:** those matching inclusion criteria between April 2004 and April 2013 at a single centre.
Prognostic variable	RVEF per 5% higher (continuous variable) on CMR (continuous variable, no referent) RVEF <46% on CMR RVEF ≥46% on CMR (referent)

	RV-ESVI per 10 ml/m^2 higher (continuous variable) on CMR (continuous variable, no referent) RV-ESVI ≥76 ml/m^2 on CMR RV-ESVI <76 ml/m^2 on CMR (referent) RV-EDVI on CMR – continuous variable but increment used is unclear (no referent) TR fraction on CMR – continuous variable but increment used is unclear (no referent) All patients underwent CMR within 1 month prior to surgery. Performed using 1.5T system using standard protocols. Same imaging unit used for all patients. Steady-state free-precession cine images obtained with breath hold to visualise ventricular wall motions. Entire short-axis images acquired at 6 mm interval with a 4 mm intersection gap from valve plane to apex to include whole ventricular volume. RV and LV end-diastolic volume and end-systolic volume, stroke volumes, cardiac output and ejection fractions were measured using software. Ventricular volumes and cardiac output were normalised for body surface area. TR amount was calculated by subtracting net pulmonary blood volume from RV stroke volume. TR fraction calculated by dividing TR amount by RV stroke volume. Analysis of cardiac MR images was performed by two experienced observers who were blinded to clinical data.
Confounders	Univariate/multivariate Cox proportional hazards model. Variables with univariate P-value <0.10 were incorporated into multivariate models. Factors included in adjusted analysis (applies for cardiac death and major postoperative cardiac events outcomes): • Continuous RVEF variable: age, sex, NYHA class, haemoglobin level and glomerular filtration rate • Threshold RVEF variable (<46%): unadjusted and estimated from Kaplan-Meier plots • Continuous RV-ESVI variable: age, sex, NYHA class, haemoglobin level and glomerular filtration rate • Threshold RV-ESVI variable (≥76%): unadjusted and estimated from Kaplan-Meier plots • Continuous RV-EDVI variable: unadjusted as only univariate results reported • Continuous TR fraction variable: unadjusted as only univariate results reported For those that were adjusted (continuous RVEF variable and continuous RV-ESVI variable models), age was adjusted for in the model, which was the only confounder prespecified for postoperative mortality and unplanned hospital admission. Other listed prognostic variables were unadjusted only and therefore had not adjusted for age.
Outcomes and effect sizes	**Cardiac death following TR surgery**

	RVEF on CMR **HR 0.714 (95% CI 0.528 to 0.966, P=0.029) for RVEF per 5% higher (analysed as a continuous variable) on CMR** – adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate **HR 5.06 (95% CI 1.56 to 16.46, P=0.007) for RVEF <46% vs. RVEF ≥46% on CMR** – unadjusted, estimated from data provided RV-ESVI on CMR **HR 1.183 (95% CI 1.025 to 1.365, P=0.021) for RV-ESVI per 10 ml/m^2 higher (analysed as a continuous variable) on CMR**– adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate **HR 0.29 (95% CI 0.09 to 0.91, P=0.034) for RV-ESVI ≥76 ml/m^2 vs. RV-ESVI <76 ml/m^2 on CMR** – unadjusted, estimated from data provided RV-EDVI on CMR **HR 1.008 (95% CI 0.999 to 1.017, P=0.076) for RV-EDVI on CMR as a continuous variable (increment unclear)** – unadjusted TR fraction on CMR **HR 0.985 (95% CI 0.953 to 1.019, P=0.395) for TR fraction on CMR as a continuous variable (increment unclear)** – unadjusted **Major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery** RVEF on CMR **HR 0.795 (95% CI 0.649 to 0.974, P=0.027) for RVEF per 5% higher (analysed as a continuous variable) on CMR** – adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate **HR 3.94 (95% CI 1.59 to 9.76, P=0.003) for RVEF <46% vs. RVEF ≥46% on CMR** – unadjusted, estimated from data provided RV-ESVI on CMR **HR 1.102 (95% CI 0.997 to 1.218, P=0.057) for RV-ESVI per 10 ml/m^2 higher (analysed as a continuous variable) on CMR** – adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate

	HR 0.46 (95% CI 0.19 to 1.11, P=0.029) for RV-ESVI ≥76 ml/m^2 vs. RV-ESVI <76 ml/m^2 on CMR – unadjusted, estimated from data provided RV-EDVI on CMR **HR 1.005 (95% CI 0.998 to 1.012, P=0.163) for RV-EDVI on CMR as a continuous variable (increment unclear)** – unadjusted TR fraction on CMR **HR 0.986 (95% CI 0.960 to 1.013, P=0.293) for TR fraction on CMR as a continuous variable (increment unclear)** – unadjusted During follow-up, 13 patients died due to cardiac reasons (n=8 due to heart failure, n=1 due to infective endocarditis, n=1 due to ventricular fibrillation and n=3 were sudden cardiac deaths). There were a further 7 non-cardiac deaths (n=3 due to pneumonia, n=1 due to mediastinitis, n=1 due to intracranial haemorrhage, n=1 due to renal failure and n=1 due to malignancy). Of the 55 patients that did not die, n=6 and n=8 experienced unplanned readmission for cardiovascular problems within 1 year and 5 years, respectively. The 5-year survival and 5-year event-free survival rates were 76.0% (57/75) and 65.3% (49/75), respectively. Cardiac deaths occurred in 8/23 (34.8%) of those with RVEF on CMR <46% and in 5/52 (9.6%) of those with RVEF on CMR ≥46%. Major postoperative cardiac events occurred in 12/23 (52.2%) of those with RVEF <46% and in 10/52 (19.2%) of those with RVEF ≥46%. Follow-up was performed by clinical visits, medical record review and telephone contact and was complete in 100% of patients. All medical records reviewed by independent research nurse and telephone interviews arranged if needed to monitor development of clinical events. Institutional database was matched to nationwide official data on death certification provided by National Statistical Office to validate accuracy of mortality information. Primary endpoint was cardiac death. All-cause mortality and unplanned readmission due to cardiovascular problems at follow-up were also collected. Composite outcome of major postoperative cardiac events was defined as cardiac death or unplanned cardiac-related readmission. Median (IQR) follow-up following surgery: 57 (21-82) months
Comments	**Cardiac death following TR surgery** RVEF on CMR – continuous, adjusted variable Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW

4. Outcome Measurement	HIGH
5. Study confounding	LOW
6. Statistical analysis	HIGH
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
- Outcome – only includes cardiac deaths in the analysis rather than any mortality

<u>RVEF on CMR – threshold (<46% vs. ≥46%), unadjusted variable</u>

Risk of bias:

1. Study participation	LOW
2. Study attrition	LOW
3. Prognostic factor measurement	LOW
4. Outcome Measurement	HIGH
5. Study confounding	VERY HIGH
6. Statistical analysis	HIGH
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
- Outcome – only includes cardiac deaths in the analysis rather than any mortality
- Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

<u>RV-ESVI on CMR – continuous, adjusted variable</u>

Risk of bias:

1. Study participation	LOW
2. Study attrition	LOW

3. Prognostic factor measurement	LOW
4. Outcome Measurement	HIGH
5. Study confounding	LOW
6. Statistical analysis	HIGH
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
- Outcome – only includes cardiac deaths in the analysis rather than any mortality

<u>RV-ESVI on CMR – threshold (≥76 ml/m^2 vs <76 ml/m^2), unadjusted variable</u>

Risk of bias:

1. Study participation	LOW
2. Study attrition	LOW
3. Prognostic factor measurement	LOW
4. Outcome Measurement	HIGH
5. Study confounding	VERY HIGH
6. Statistical analysis	HIGH
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
- Outcome – only includes cardiac deaths in the analysis rather than any mortality
- Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

<u>RV-EDVI on CMR – continuous, unadjusted variable</u>

Risk of bias:

1. Study participation	LOW

2. Study attrition	LOW
3. Prognostic factor measurement	HIGH
4. Outcome Measurement	HIGH
5. Study confounding	VERY HIGH
6. Statistical analysis	LOW
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
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- Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

<u>TR fraction on CMR – continuous, unadjusted variable</u>

Risk of bias:

1. Study participation	LOW
2. Study attrition	LOW
3. Prognostic factor measurement	HIGH
4. Outcome Measurement	HIGH
5. Study confounding	VERY HIGH
6. Statistical analysis	LOW
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
- Prognostic factor – effective regurgitant orifice area listed in protocol and TR fraction is not the same as this.
- Outcome – only includes cardiac deaths in the analysis rather than any mortality

- Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery

RVEF on CMR – continuous, adjusted variable

Risk of bias:

1. Study participation	LOW
2. Study attrition	LOW
3. Prognostic factor measurement	LOW
4. Outcome Measurement	HIGH
5. Study confounding	LOW
6. Statistical analysis	HIGH
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
- Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately.

RVEF on CMR – threshold (<46% vs. ≥46%), unadjusted variable

Risk of bias:

1. Study participation	LOW
2. Study attrition	LOW
3. Prognostic factor measurement	LOW
4. Outcome Measurement	HIGH
5. Study confounding	VERY HIGH
6. Statistical analysis	HIGH
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
- Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately.
- Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality and readmission for cardiac reasons. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

<u>RV-ESVI on CMR – continuous, adjusted variable</u>

Risk of bias:

1. Study participation	LOW
2. Study attrition	LOW
3. Prognostic factor measurement	LOW
4. Outcome Measurement	HIGH
5. Study confounding	LOW
6. Statistical analysis	HIGH
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
- Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately.

<u>RV-ESVI on CMR – threshold (≥76 ml/m^2 vs <76 ml/m^2), unadjusted variable</u>

Risk of bias:

1. Study participation	LOW
2. Study attrition	LOW
3. Prognostic factor measurement	LOW
4. Outcome Measurement	HIGH
5. Study confounding	VERY HIGH
6. Statistical analysis	HIGH
7. Other risk of bias	LOW

OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

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- Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately.
- Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality and readmission for cardiac reasons. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

<u>RV-EDVI on CMR – continuous, unadjusted variable</u>

Risk of bias:

1. Study participation	LOW
2. Study attrition	LOW
3. Prognostic factor measurement	HIGH
4. Outcome Measurement	HIGH
5. Study confounding	VERY HIGH
6. Statistical analysis	LOW
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
- Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately.
- Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality and readmission for cardiac reasons. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

<u>TR fraction on CMR – continuous, unadjusted variable</u>

Risk of bias:

1. Study participation	LOW
2. Study attrition	LOW

	3. Prognostic factor measurement	HIGH
	4. Outcome Measurement	HIGH
	5. Study confounding	VERY HIGH
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.
- Prognostic factor – effective regurgitant orifice area listed in protocol and TR fraction is not the same as this.
- Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately.
- Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality and readmission for cardiac reasons. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.